REMARKS

Claims 1-2 and 8-12 and 50 are pending in this application. Applicant respectfully requests reconsideration of the above–identified application in view of the argument below.

In the Office Action, the Examiner includes a new ground of rejection (Item 2, below) that was not necessitated by Applicant's amendment of the claims or information submitted in an IDS. Pursuant to MPEP § 706.07(a, c & d), the Applicant contends the final rejection presented is premature, and requests that the Examiner reconsider the finality of the last action.

CLAIM OBJECTIONS

Applicant notes that the Examiner has maintained the rejection of claims 1-2, 8-12 and claim 50 under 35 U.S.C. § 112, first paragraph for the reasons set forth on pages 2-8 of the previous Office Action. The Examiner also provides additional basis for rejection of these claims. Applicant traverses these rejections for the following reasons.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. (MPEP § 2164.01).

1. **The Examiner has not met her burden.** As set forth in MPEP § 2164.04, the burden is on the Examiner under the enablement requirement to establish a reasonable basis to question the enablement provided for the claimed invention. The teaching in the specification must be taken to be in compliance with the enablement requirements of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

As discussed in the MPEP § 2164.05, the language of the Examiner's rejection should focus on those factors, reasons and evidence that lead the Examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation. The Examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue

experimentation. References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. However, technical reasons are always required. MPEP § 2164.05, and *In re Marzocchi, supra*.

2. "Test Agents." First, Examiner indicates that the specification fails to enable a method of screening for an agent that modulates bone mineralization because the specification fails to disclose *specific* test agents to be used in the claimed method." (Office Action, page 3-4).

The Examiner raises this ground for rejection for the first time in this final Office Action, therefore, as stated above Applicant requests that the Examiner reconsider the finality of the last action.

The Examiner claims that the specification's lack of specific test agents renders the claims non-enabling. In response, Applicant respectfully points to the discussion noted in part by the Examiner describing classes of "test agents" which may be useful in the invention. The specification indicates, for example:

> "The [test] agent can be virtually any chemical compound. It can exist as a single isolated compound or can be a member of a chemical (e.g. combinatorial) library. In a particularly preferred embodiment, the test agent will be a small organic molecule." (Spec., page 9).
>
> In certain embodiments, the test agent is not an antibody and/or not a protein and/or not a nucleic acid. ." (Spec., pages 3, 4)

The specification also discuses by way of example up regulating expression of NELL-1 gene by affecting the gene promoter. (Spec., page 4) The specification also discloses methods for "prescreening" test agents for use in the screening method by using binding assays, which are well known to those in the art. (Spec., pages 10, 28) Finally, the specification discusses the generation of combinatorial libraries for screening, which are well known in the art (Spec., page 30).

Applicant respectfully notes that the Examiner has not provided a specific technical reason to doubt the adequacy of the cited teachings provided in the specification. Applicant also contends that undue experimentation would not be required for one skilled in the art to select test agents to use in the claimed screening method.

Considering the evidence of the *Wands* factors as a whole set forth, but not discussed by the Examiner in the prior Office Action (pages 4-5): 1) the quantity of experimentation to determine a test agent which induces mineralization is not undue as it is routine experimentation to assay various agents and quantify the effect on mineralization; 2) the Applicant renders significant guidance as to the selection of types of test agents and methods of pre-screening for test agents which may be effective in the screening method claimed; 4) the nature of the invention is one for screening for agents which modulate NELL-1 expression, consequently all test agents can not be expected to be known and disclosed; 5) the state of the art includes methods for "prescreening" agents, and for detecting changes in mineralization, therefore all of the methods needed to practice the invention are known; 6) there was a high level of skill in the art at the time the application was filed; 7) the pre-screening methods suggested by the Applicant significantly improve the predictability that test agents will affect the NELL-1 gene expression, and one skilled in the art would have viewed other classes of molecules known to play a role in mineralization and bone formation as logical test agent candidates; 8) the breadth of the claim is supported by the anticipated result of screening test agents for modulation or mineralization.

The Examiner states only that the lack of specific test agents renders the claims not enabled. However, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the *Wands* factors while ignoring the others (MPEP § 2164.01(a)). As is the cases here, where all other factors point toward enablement, then the absence of a specific working example will not by itself render the invention non-enabled (MPEP § 2164.02). Therefore, Applicant requests that the Examiner withdraw this rejection as a basis for non-enablement.

3. Modulation of mineralization.

a. Function of NELL-1. Second, the Examiner indicates that "one of skill in the art could not conclude that the claimed method of screening for an agent that modulates bone mineralization in an osteogenic cell containing NELL-1 gene can be obtained by the information contained in the instant disclosure." (Office Action, page 4).

Applicant respectfully reiterates that the Examiner's assumption that Ting et al. (1999) and Zhang et al. (2002) are prior art references is incorrect. With respect to Ting et al. (1999), the Examiner has previously acknowledged the receipt of the Ting Declaration submitted under 37 U.S.C. § 1.131 and Exhibit, and subsequently withdrew rejections under 35 U.S.C. § 102 and § 103 based thereon. (Office Action dated 7/15/2003). With respect to Zhang, et al. (2002), clearly an article published 3 years after the filing date is not prior art to the present application.

The Examiner also states that, "The function of NELL-1 can not be ascertained by the instant disclosure." (Office Action, page 4). This statement is in clear contradiction to the teachings of the specification and the prosecution record. The specification specifically demonstrates that increasing the expression of NELL-1 increases bone mineralization in rat calvarial primary cell cultures and MC3T3 cultures, an osteoblastic cell line. (Spec., page 41-42 and FIG. 1A & B, for example). Further, the Examiner has previously stated in the record that, "... one of ordinary skill in the art could reasonably conclude that the protein encoded by NELL-1 enhances bone mineralization." (Paper 14, page 7) Therefore, Examiner's current position on this issue is untenable, and the Examiner's references to the mechanism of NELL-1 action on mineralization are insufficient to refute the clear teachings of the specification. That the *mechanism* of action NELL-1 was discussed in the specification, but not specifically determined, is of no consequence to the patentability of the pending claims.

b. Modulation of NELL-1. Third, the Examiner indicates that, "There is lack of enablement for the use of the method for screening an agent that *modulates* bone mineralization because the specification merely focuses on the *enhancement* of the NELL-1 gene in calvarial osteoblastic cells. ... It is determined that there are no working examples commensurate with the claims that demonstrate that a *reduction* in NELL-1 expression corresponds with decreased bone mineralization and there is limited guidance provided in the specification as to how to use the claimed method. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as claimed." (Office Action, page 5, emphasis added).

As stated, the specification discloses the effect of increasing NELL-1 expression on increased mineralization. However, the specification also discloses that the method is intended for identifying agents that modulate (e.g., *up-regulate* and *down-regulate*) NELL-1 expression. (Spec., page 10, emphasis added). The specification further discusses screening methods to detect either increases or decreases in mineralization. (Spec., page 11). The Examiner has failed to state any technical reason for why the specification is not enabling for test agent which modulate mineralization (i.e., up-regulate or down-regulate mineralization).

Of note, the Examiner does not specifically dispute Applicant's contention that mineralization occurs in both intramembraneous and endochonral bone, and consequently, NELL-1 expression in osteogenic cells generally may effect mineralization in osteogenic cells.

Specifically, the Examiner presents no technical argument as to why osteogenic cells from calvaria (involved in "intramembranous ossification") or non-calvaria (e.g., femur, tibia) involved in "endochondral ossification" are distinct in their response to osteogenic stimuli. In fact, those skilled in the art would have understood mineralization to occur in both of these main bone types, since endochondral bone also involves the process of intramembranous ossification during skeletal development and during long bone fracture repair (Caplan AI, and Boyan B. Endochondral bone formation: The lineage cascade. In Bone volume 8: Mechanism of bone development and growth. BK Hall, editor. Boca Raton: CRC Press, Inc. 1-46, 1994).

Further, Kuberasampath (US Pat. No. 5,674,844), discloses that fetal or newborn rat calvaria cells represent a "heterogeneous [population] having individual cells at different stages of differentiation, [and that] the culture is believed to more accurately reflect the metabolism and function of osteoblasts *in vivo* than osteoblast culture obtained from established cell lines," and these cells are commonly used as a model in this field. Furthermore, the art also recognizes that "osteogenic cells" include "osteoblasts, osteoblast like cells, mesenchymal cells, fibroblast cells, fetal embryonic cells, stem cells, bone marrow cells, dura cells, chondrocytes, and chondroblastic cells and fetal calvarial osteoblastic cell, or cell lines, such as MC3T3 cells," (such as disclosed at Spec. page 8,

33-34). Furthermore, because fetal or newborn calvarial cells represent a heterogeneous population, they are not meant to be limiting in terms of the cell type or cellular differentiation state or of the osteogenic potential in this invention.

Finally, a review of issued patents for osteogenic or mineralizing substances reveals that osteogenic screening assays utilizing fetal rat calvarial cells were sufficient to support claims regarding bone formation without distinction between calvarial and non-calvarial sources of osteogenic osteoprogenitor cells (See for example, US Pat. Nos. 6,462,019, 6,413,998, 6,352,972). Therefore, for the representative example of NELL-1 expression in fetal calvarial osteoblastic cells and MC3T3 osteoblastic cell line affecting mineralization is sufficient to support the breadth of the claim drawn to a screening method of osteogenic cells.

Therefore, Applicants contend that undue experimentation would not be required for one skilled in the art to determine whether NELL-1 may be expressed in a particular osteogenic cell type, nor measure the effect upon mineralization caused by the modulation of NELL-1 in the claimed screening method. In addition to the Wands factors previously discussed, the methods of detecting gene expression and measuring mineralization are techniques well within the purview of the level of skill in the art

For the reasons already stated with respect to the analysis of the *Wands* factors, and the teachings described in the specification, Applicant requests that the Examiner withdraw this rejection as a basis for non-enablement.

4. Summary. Applicant respectfully maintains that the teachings of the specification, in combination with knowledge of those skilled in the art, provide ample guidance to enable those skilled in the art to make and use the invention. Because the Examiner has not met the burden under the enablement requirement, and in view of the arguments set forth above, the rejection of claims 1-2, 8-12 and 50 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CONCLUSION

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of

this paper, including extension of time fees, to Deposit Account 501946 and please credit any excess fees to such deposit account; please reference attorney docket no. 38586-329.

Respectfully submitted,
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